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EXAMINER	
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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,182	ISHIHARA, TAKASHI	
	Examiner	Art Unit	
	David A. Saunders	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/13/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-92* is/are rejected.

7)☒ Claim(s) *93-98* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :9/29/05,11/15/05,6/13/06,9/5/06,8/31/07.

AMENDMENT ENTRY

Amendment of 2/13/08 has been entered. Claims 60-98 are pending. Claims 60-98 are under consideration.

RESPONSE TO ELECTION/RESTRICTION

Applicant's election without traverse of Group IV (claims 60-98) in the reply filed on 2/13/08 is acknowledged.

OBJECTION(S) TO CLAIMS

Claims 93 and 95 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Claim 93 depends from multiple dependent claim 92. Claim 95 depends from multiple dependent claims 67, 74, 81, 88, 92 and 93. See MPEP § 608.01(n). Accordingly, claims 93-98 have not been further treated on the merits. The examiner fails to see why it is necessary for any of claims 74, 81, 88, 92 or 93 to be multiple dependent, since reference to "step (3)" in claims 74, 81 and 88 would be understood to refer back to "step (3)" of the independent claim in the chain of dependencies, and since reference to "step (2)" and to "step (1)" in claims 92 and 93 would be understood to refer back to "step (2)" and to "step (1)" of the independent claim in the chain of dependencies.

REJECTION(S) UNDER 35 USC 112, SECOND PARAGRAPH

Claims 66-70, 73-77, 80-84, 88-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 66, in each of lines 2-4, "the antibody containing solution" lacks antecedent basis, since no "solution" has been previously recited. Like rejections apply to claims 73, 80 and 87.

In claim 67, line 2 "following step (3) of claim 64" is confusing, because claim 67 depends from claim 60, via claim 66; neither of claims 60 nor 66 have a "step (3)".

In each of claims 69-70 "the pH level" lacks antecedent basis, since no such "level" has been previously recited. Like considerations apply to claims 76-77, 83-84 and 90-91.

REJECTION(S) UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 60-61, 63 and 66 are rejected under 35 U.S.C. 102(b) as being entirely anticipated by Williams et al WO 00/01822, cited on PTO-892).

Williams et al teach the separation of a human IgG1 antibody from bovine IgG (which is present due to culturing of antibody producing cells in media containing fetal calf serum) via protein A affinity chromatography. The mixture of human IgG1 antibody and bovine IgG is applied to the column in PBS. The bovine IgG is then eluted at pH 4.5. The human IgG1 antibody is then eluted at pH 3.5. See Example 4, under "Purification of Antibodies".

Thus instant claims 60-61 are anticipated.

The above noted sequence of adding elution buffers constitutes a "stepwise" lowering of pH, In accord with claim 63.

Regarding claim 66, the cell culture supernatants were clarified by centrifugation and filtration through a 0.22 um membrane; this filtration step constitutes "aseptic filtration", in accord with instant claim 66.

REJECTION(S) UNDER 35 USC 102/103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 60-61, 63 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Hardman et al (6,066,718, cited on PTO-892).

Hardman et al teach a method in which COS cells express and secrete an IgG1 humanized antibody. Hardman et al teach a method of separating the humanized antibody from COS cell supernatants. The COS cell supernatants are loaded onto a ProSep A (Protein A) column that has been equilibrated with PBS buffer (20 mM NaPhos, 150 mM NaCl) at pH 8.0. The Prosep A column is then further washed with PBS buffer. Then the column is washed with 100 mM NaCitrate buffer at pH 5.0, in order to elute bovine IgG (From fetal bovine serum used in culturing). Then the column is washed with 100 mM NaCitrate buffer at pH 3.0, in order to elute humanized antibodies. See Example 6. Thus instant claims 60-61 are anticipated, if the term "human antibody" encompasses a "humanized antibody".

The above noted sequence of adding elution buffers constitutes a "stepwise" lowering of pH, In accord with claim 63.

Regarding claim 66, the COS cell supernatants were clarified by filtration through a 0.45 um membrane; this step constitutes "aseptic filtration", in accord with instant claim 66.

If the term "human antibody" does not encompass a "humanized antibody", then the method of differentially eluting bovine IgG and a human antibody would have been completely obvious. Because the IgG1 humanized antibody of Hardman et al has a fully human IgG1 isotype in its Fc region, and because it was art known that Protein A binds

any immunoglobulin according to its isotype in the Fc region, one would have fully expected that the method of Hardman et al would likewise separate bovine IgG and a human antibody.

Claims 60-61, 63 and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Chestnut et al (5,800,815, cited on PTO-892).

Chestnut et al teach a method in which CHO cells express and secrete an IgG4 humanized antibody. Chestnut et al teach a method of separating the humanized antibody from CHO cell supernatants. The CHO cell supernatants are loaded onto a Protein A column. The Protein A column is then washed with PBS buffer. Then the column is washed with 0.2 M NaAc buffer at pH 4.5, in order to elute bovine IgG (From fetal bovine serum used in culturing). Then the column is washed with 0.2 M Glycine, 0.5 M NaCl at pH 3.5, in order to elute humanized antibodies. See espec. Col. 40, lines 39-50 and col. 42, lines 52-64. Thus instant claims 60-61 are anticipated, if the term "human antibody" encompasses a "humanized antibody".

The above noted sequence of adding elution buffers constitutes a "stepwise" lowering of pH, In accord with claim 63.

Regarding claim 66, the CHO cell supernatants were clarified by filtration through a 0.45 um membrane; this step constitutes "aseptic filtration", in accord with instant claim 66.

If the term "human antibody" does not encompass a "humanized antibody", then the method of differentially eluting bovine IgG and a human antibody would have been completely obvious. Because the IgG4 humanized antibody of Chestnut et al has a fully human IgG4 isotype in its Fc region, and because it was art known that Protein A binds any immunoglobulin according to its isotype in the Fc region, one would have fully expected that the method of Chestnut et al would likewise separate bovine IgG and a human antibody.

Claims 60-62 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Umana et al (2004/0241817, cited on PTO-892).

Umana et al teach a method that uses a pH gradient for separately eluting bovine and human IgGs from Protein A. See page 29, para. [0274]. Thus instant claims 60-62 are anticipated.

Should applicant urge that the exemplified antibodies may be chimeric, rather than human antibodies, then the method of differentially eluting bovine IgG and a human antibody would have been completely obvious. Because the IgG1 chimeric antibody of Umana et al has a fully human IgG1 isotype in its Fc region, and because it was art known that Protein A binds any immunoglobulin according to its isotype in the Fc region, one would have fully expected that the method of Umana et al would likewise separate bovine IgG and a human antibody. Further, it is considered that because Umana et al recite "a pH-gradient elution that effectively separates bovine and human IgGs", Umana et al had actually separated bovine and fully human IgGs or, else, fully expected that their method would effectively separate bovine and fully human IgGs

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 60-62 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Moellering et al (BioPharm 1990, cited on PTO-892).

Moellering et al teach a method of separating a chimeric IgG and bovine IgG via gradient elution from a Protein A HPLC column. See Fig 3. Even though the Protein A HPLC column is used for analytical, rather than preparative purposes, the claims are anticipated because, in either case, the Protein A HPLC column effects a "separating" of human antibodies and ungulate antibodies. Thus instant claims 60-62 are anticipated.

Should applicant urge that the exemplified antibodies are chimeric rather than human antibodies, then the method of differentially eluting bovine IgG and a human

antibody would have been completely obvious. Because the IgG chimeric antibody of Moellering et al has a fully human IgG isotype in its Fc region, and because it was art known that Protein A binds any immunoglobulin according to its isotype in the Fc region (p 35, col. 2), one would have fully expected that the method of Moellering et al would likewise separate bovine IgG and a human antibody, in cases in which one wanted to monitor the separation of a fully human antibody from a culture medium containing bovine IgG.

REJECTION(S) UNDER 35 USC 103

Claims 64-65, 71-73, 78-80 and 85-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umana et al in view of Leibl et al (BioPharm 1990, cited on PTO-892) and anyone or more of Williams et al, Hardman et al, or Chestnut et al.

Umana et al have been cited supra for teaching a method that uses a pH gradient for separately eluting bovine and human IgGs from Protein A. They do not give details as to the buffers used, or even the pHs at which bovine and human IgGs may elute.

Leibl et al teach that a buffer of 0.1 M disodium phosphate, 0.1 M NaAc, 0.1 M glycine, and 0.15 M NaCl can be used as a loading buffer for human IgGs onto Protein-A and that bound IgGs of different subclasses can be eluted with a linear gradient from pH 8.1 to pH 2.8. Williams et al teach that bovine IgG is then eluted at pH 4.5 and that human IgG1 antibody is then eluted at pH 3.5. Hardman et al teach that a buffer at pH 5.0 elutes bovine IgG and that a buffer at pH 3.0 elutes humanized antibodies. Chestnut et al teach that a buffer at pH 4.5 elutes bovine IgG and that a buffer at pH 3.5 elutes humanized antibodies. All of Williams et al, Hardman et al and Chestnut et al load at a pH value near the upper end of the pH gradient used by Leibl et al (PBS has a pH around 7.2-7.4). Also, all of the elution pH values given by Williams et al, Hardman et al, and Chestnut et al fall within the range at which Leibl et al used their linear gradient to elute bound human IgGs of different subclasses. Since the difference between the pH value that elutes bovine IgG and the pH value that elutes human/humanized antibodies shown by any of Williams et al, Hardman et al, or Chestnut et al, is greater than the pH

difference of 0.5-0.7 pH units that Leibl et al observed would separate human IgG into different peaks (p 53, col. 2), one would have fully expected that the buffer system used by Leibl et al would effectively separate bovine and human IgGs according to a gradient elution method like that of Umana et al.

Claims 66-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Williams et al, Hardman et al, or Chestnut et al, or Umana et al, as applied to claim 60 above, and further in view of Shadle et al (5,429,746, cited on PTO 1449 of 9/29/05).

Each of the primary references has been cited further supra for teaching the stepwise or gradient elution of bovine IgG and human/humanized IgG from a Protein-A column. Each of these references teaches that the human/humanized IgG is to be used in vivo. Shadle et al show that when immunoglobulin preparations, including those from cell culture (col. 4, lines 17-32), are prepared for in vivo use, it is conventional to conduct viral inactivation and aseptic filtration as recited in claim 66. Shadle et al show the pH and time limitations of instant claim 67 at col. 13, lines 6-10. Shadle et al also show aseptic filtration, through a 0.2 um filter, as a final step, as recited in instant claim 68; see Fig. 1.

Irrespective of whether or not Shadle et al teach anything about stepwise or gradient elution of bovine IgG and human/humanized IgG from Protein-A, it would have been obvious to add the conventional steps of viral inactivation and aseptic filtration, following the separation of bovine IgG and human/humanized IgG from Protein-A. Not only would such steps have been obvious, they would have been required by regulatory authorities that would approve any human/humanized antibody for in vivo use.

Claims 73-77, 80-84 and 85-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umana et al in view of Leibl et al and any of Williams et al, Hardman et al, or Chestnut et al, as applied to claims 71, 78 and 85 above, and further in view of Shadle et al (5,429,746, cited on PTO 1449 of 9/29/05).

Umana et al has been cited in combination with Leibl et al and any of Williams et al, Hardman et al, or Chestnut et al further supra for teaching the gradient elution of bovine IgG and human/humanized IgG from a Protein-A column. All of these references teach that the and human/humanized IgG is to be used in vivo.

Shadle et al are cited as in the rejection of claims 66-70 supra for showing that it would have been obvious to add the conventional steps of viral inactivation and aseptic filtration, following the separation of bovine IgG and human/humanized IgG on a Protein-A column.

Regarding claims 77, 84 and 91, which require a stepwise, instead of a gradient elution, these claims will be considered obvious, if one were willing to take the additional manipulative steps of conducting a stepwise, instead of a gradient, elution, since the end result of separating bovine and human IgGs would be achieved in either case.

IDS REFERENCES NOT CONSIDERED

Non-patent references lined through on attached form 1449, filed on 9/29/05, were not found in the IFW contents. The references are listed on attached form PTO-892.

ART OF INTEREST

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Robl et al (2004/0068760, cited on PTO-892) teach transgenic ungulates that produce human antibodies. As far as the examiner can determine from skimming this excessively large disclosure, there are no teachings relevant to the instant invention. Robl et al apparently envision that depletion of the host ungulate's immune system would reduce the amount of ungulate immunoglobulins present in any antiserum obtained from an immunized transgenic ungulate; therefore, there would be no need to separate ungulate and human antibodies in any antiserum thus obtained. Also Figs. 42-44 do not show use of a Protein A column for the isolation of human immunoglobulins from the transgenic ungulates.

CONTACTS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30 pm and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 5/7/08 DAS

/David A Saunders/

Primary Examiner, Art Unit 1644